# Partnerships between Academia and the Pharmaceutical Industry to Advance Green Engineering


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**U. S. Environmental Protection Agency - Region 2**

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*Adapted from the following papers:*


*Slater, Savelski, Taylor, Kiang, LaPorte, Spangler, "Pervaporation as a Green Drying Process for Solvent Recovery in Pharmaceutical Production," Paper 223f, AIChE Annual Meeting, November 2007*

*Taylor, Kiang, LaPorte, Spangler, Slater, Savelski, Hesketh, "Developing Partnerships to Advance Green Manufacturing Strategies in the Pharmaceutical Industry," Paper 37, 11th ACS Green Chem and Eng Conf, June 2007.*


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# Introduction

- Projects supported by U.S. Environmental Protection Agency – Region 2
- Pollution prevention
  - Green chemistry
  - Green engineering/green manufacturing
  - Sustainable engineering
  - Design for the environment
- Industry-University partnerships
  - Pharmaceutical sector
- Green engineering outcomes
  - P2 reductions
  - Training


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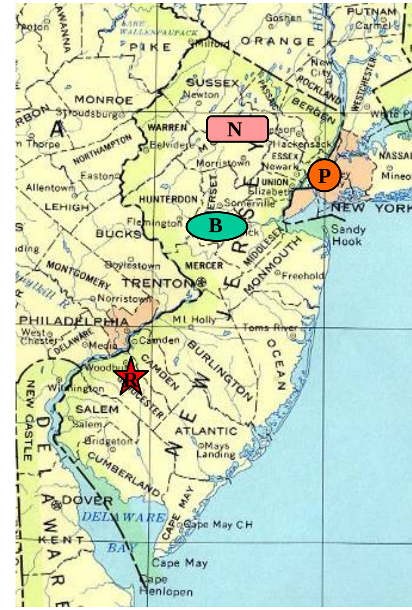
# Academic-Industrial Interaction

- Three pharmaceutical company partners
  - Bristol-Myers Squibb
  - Novartis
  - Pfizer
- Process case study or problem has a green chemistry and engineering component
- Project outcomes show P2 impact
  - Waste reduced
  - Water saved
  - Energy saved
  - Carbon footprint reduced
  - Cost saved
- "Paper-projects" / design-based, experimentally-based or combination thereof

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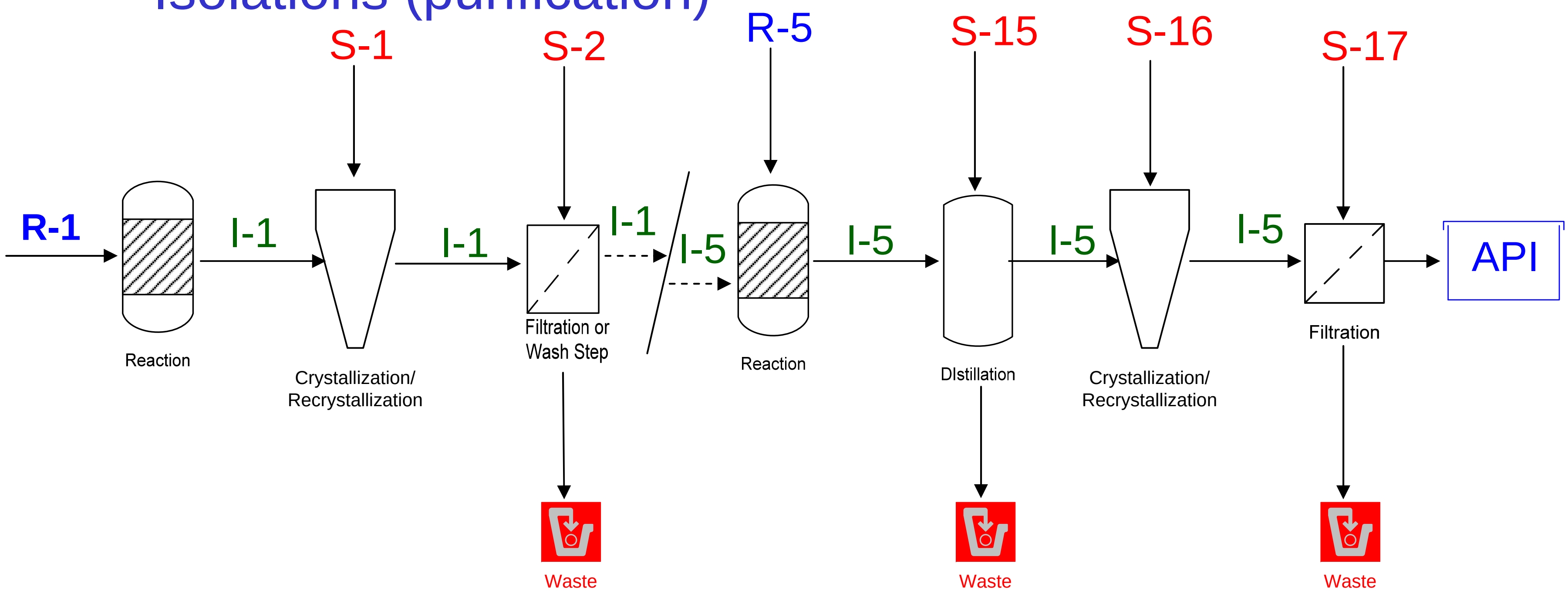
# Pharmaceutical Industry

- Highly regulated
- Long R&D timeline
- Batch processes
- High valued final product
  - API (Active Pharmaceutical Ingredient)
- High E-factor
  - High solvent use and waste generated per final product

# Typical Drug Synthesis – “Campaigns”

- Multi-step transformations – *Intermediate compounds*
- Isolations (purification)




S = Solvent – ***vary in number and complexity for each step***
R = Reactant – ***vary in number and complexity for each step***
I = Intermediate
API = Active Pharmaceutical Ingredient

# Solvent Usage

Organic solvents typically make up 60% of raw materials used*

Typical solvent usage range is 10 - 800 kg/kg API**

1 kg API

Solvent
~200 kg

*Jimenez-Gonzalez, C.; Curzons, A. D.; Constable, D.J.C.; Cunningham, V.L. Cradle-to-gate life cycle inventory and assessment of pharmaceutical compounds. Inter. J. Life Cycle Assessment 2004, 9(2), 114-121.*

*** Slater, C. S.; Savelski, M. J.; Hesketh, R.P. The selection and reduction of organic solvents in the pharmaceutical industry. Abstracts of Papers, American Chemical Society 10th Green Chem. Eng. Conf., Washington, DC, June 2006, American Chemical Society, 10.*

# Green Engineering Opportunities

- Investigate process early in development
- Green reaction strategies
- Solvent substitution – more benign solvents
- Solvent reduction – amount and variety
- Novel processes for “waste” purification / recovery
- “Telescoping” to eliminate intermediate isolations

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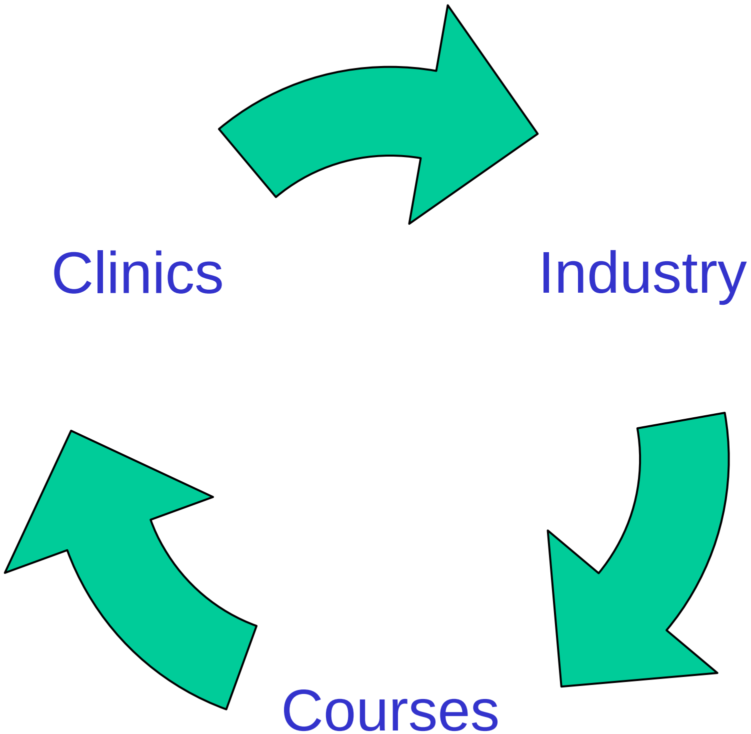
# Rowan University Clinics

- Modeled after medical schools
- Student-faculty problem solving teams
- Applied research, development, design
- Partnership: Industry, Federal/State Agency, Foundation
- Multidisciplinary
- Two 3 hour labs/wk, 1 hr/wk meeting with professor/industry
- Both semesters of Junior & Senior year and Masters students

# Rowan's Project Based Curriculum




# Clinic Timeline

- Preliminary contact
- Confidential disclosure / IP agreement
- Initial meetings: Rowan faculty/students with Process R&D scientists/engineers
- Clinic partnership agreements
- Set and review project goals/objectives
- Review of process documentation
- Site visit (plant / R&D)
- Weekly project meetings with student team
- Students interact as needed with industry partner
- End of semester presentation to industry partner

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# Industry Contributions

- Interaction with student team
- Process background and relevant information
- Connections to corporate constituencies, e.g., R&D, manufacturing, EHS
- Pharmaceutical company "culture"
- How industry prioritizes alternative strategies
- Where is the best place to improve a process
- Business sense – what will management need to see to make decisions

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# Student's Needs

- What actually goes on in a plant?
- What are the drivers that affect the evolution of a process?
- What is important and why?
- What are cGMPs and the FDA all about?
- How do we effectively work as a team?
- How do we interact with R&D, engineering, manufacturing, etc?

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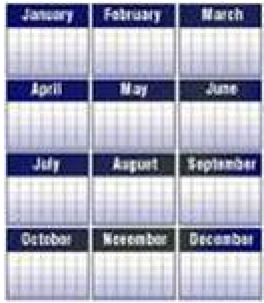
# University's Needs

- "Champion" for green engineering and partnering from industry

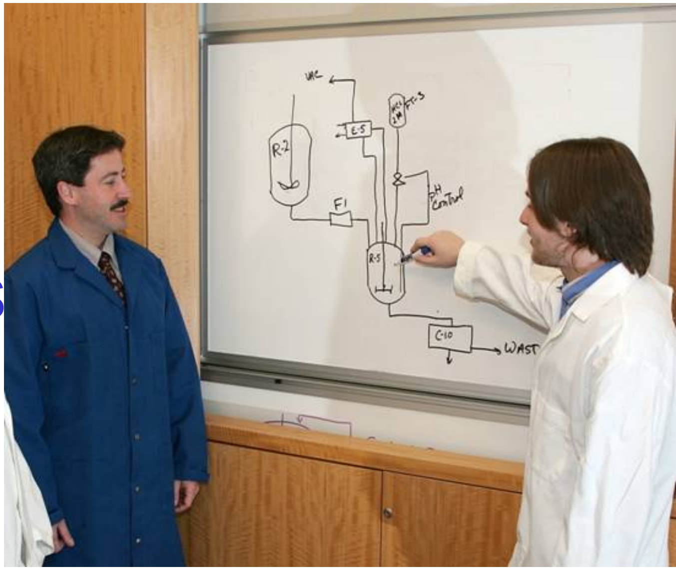
- Project matched to faculty and student expertise
- Sufficient resources allocated (time and $)




- Realistic timelines and expectations
- Reasonable confidentiality agreements – presentations/papers
- Projects that 'map' to programmatic goals/objectives, ABET criteria

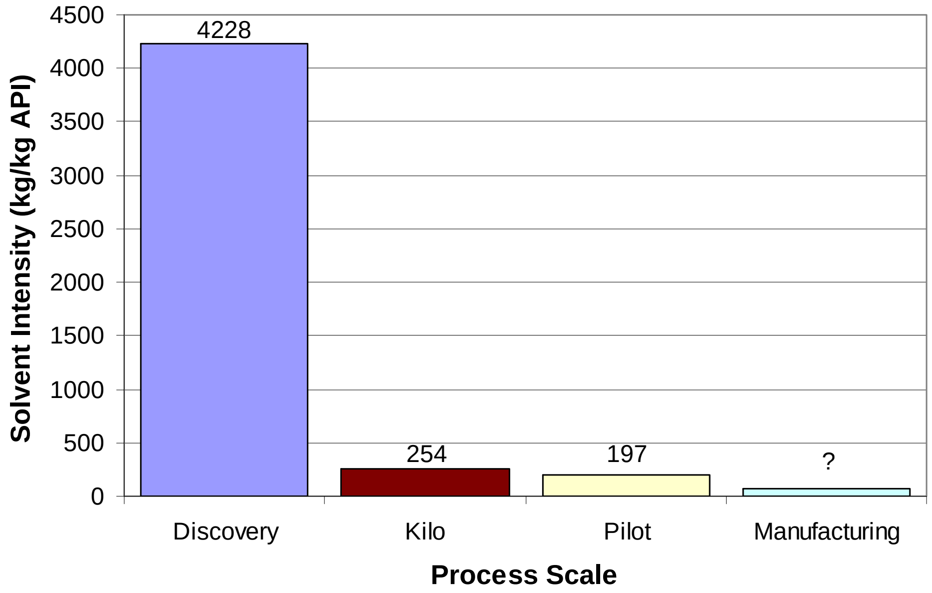
# Bristol-Myers Squibb Case Study
# "Green Drying" of Solvents

- Partnership with BMS – Process R&D (New Brunswick, NJ)
- Integration of pervaporation membrane technology for THF solvent recovery in a synthesis step of a new oncology drug
- Clinic team must make a case based Green Engineering principles and meeting pharmaceutical industry needs
- API is currently in pilot scale production for clinical trials



# Solvent issues

- Large solvent use and waste generated
  - Discovery > Pilot plant > Manufacturing
- Recovery and reuse
  - Azeotropes
  - Multiple solvents
  - Purity required
  - cGMP – FDA
  - Processing time
  - Economics




*Slater, C.S., M.J. Savelski, "A Method to Characterize the Greenness of Solvents used in Pharmaceutical Manufacture," J. Environmental Science and Health, 42, 1595-1605, 2007.*

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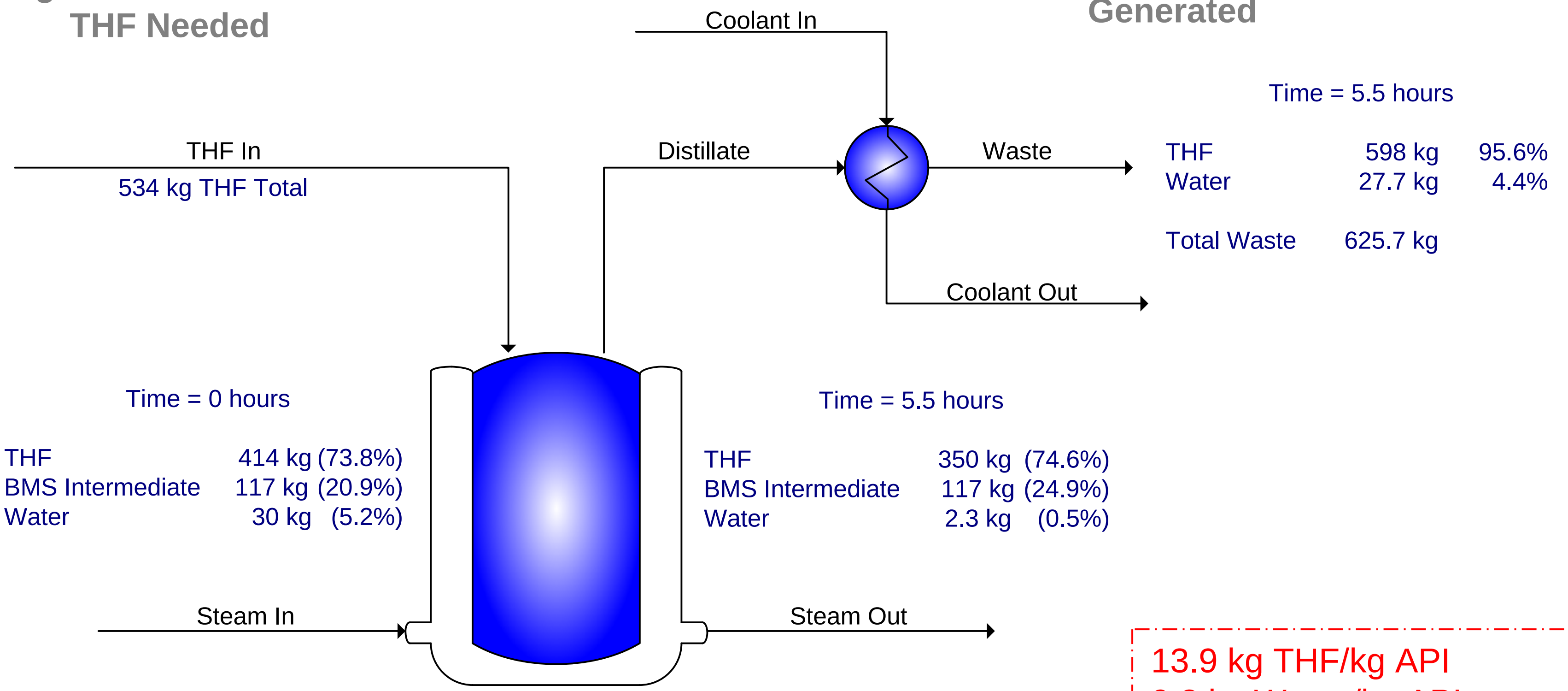
# Current Constant Volume Distillation (CVD) Process

## 68 kg API Batch Pilot-Scale

**Large Amount of Fresh THF Needed**

**Large Amount of Waste Generated**

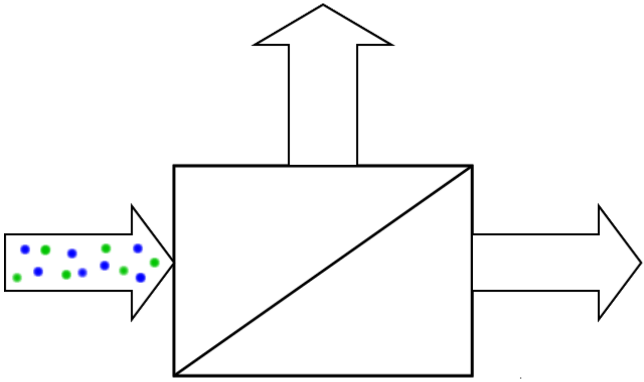



13.9 kg THF/kg API
9.2 kg Waste/kg API
7.85 kg THF Entrainer/kg API

# Pervaporation Technology

- Solvent dehydration / purification
- Azeotrope separations
- Driving equilibrium-limited reactions
- Concentrating organic mixtures
- Examples - EtOH, IPA, Acetone, DAA, EtOAc, THF, Pyridine, MEK, BuOH, etc
- Most commercialized – Sulzer systems use hydrophilic PVA membranes

Water = blue
Solvent = green



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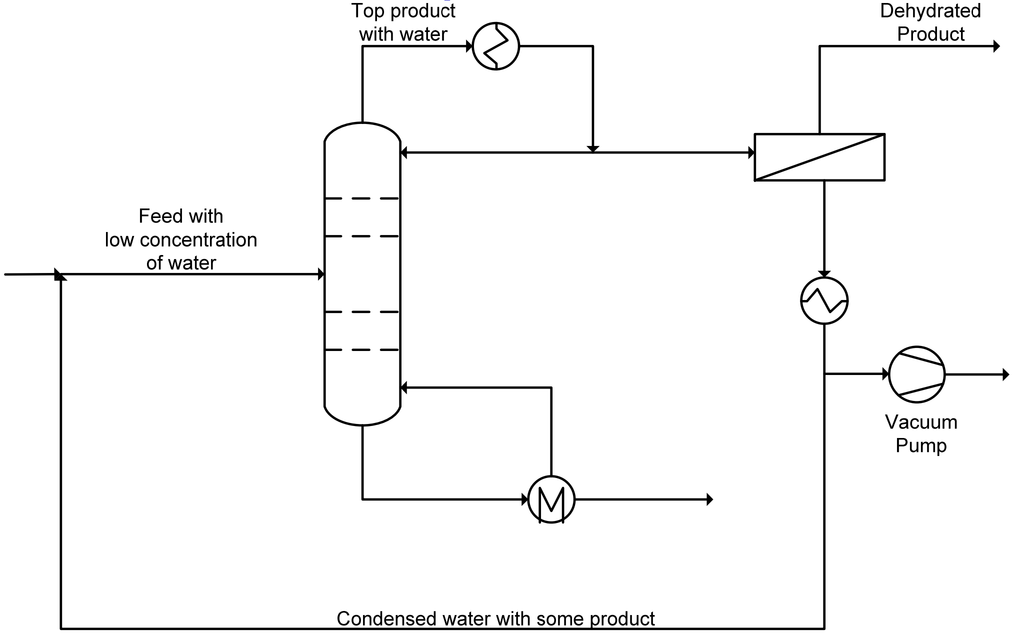
# Pervaporation Integration

- Coupling PV with distillation takes advantage of the efficiencies both operations
- Typically distillation processes exist as the conventional separation technique
- Eliminates entrainers used with azeotropic distillation
- Reduces energy consumption
- Lowers operating costs
- Easily scalable

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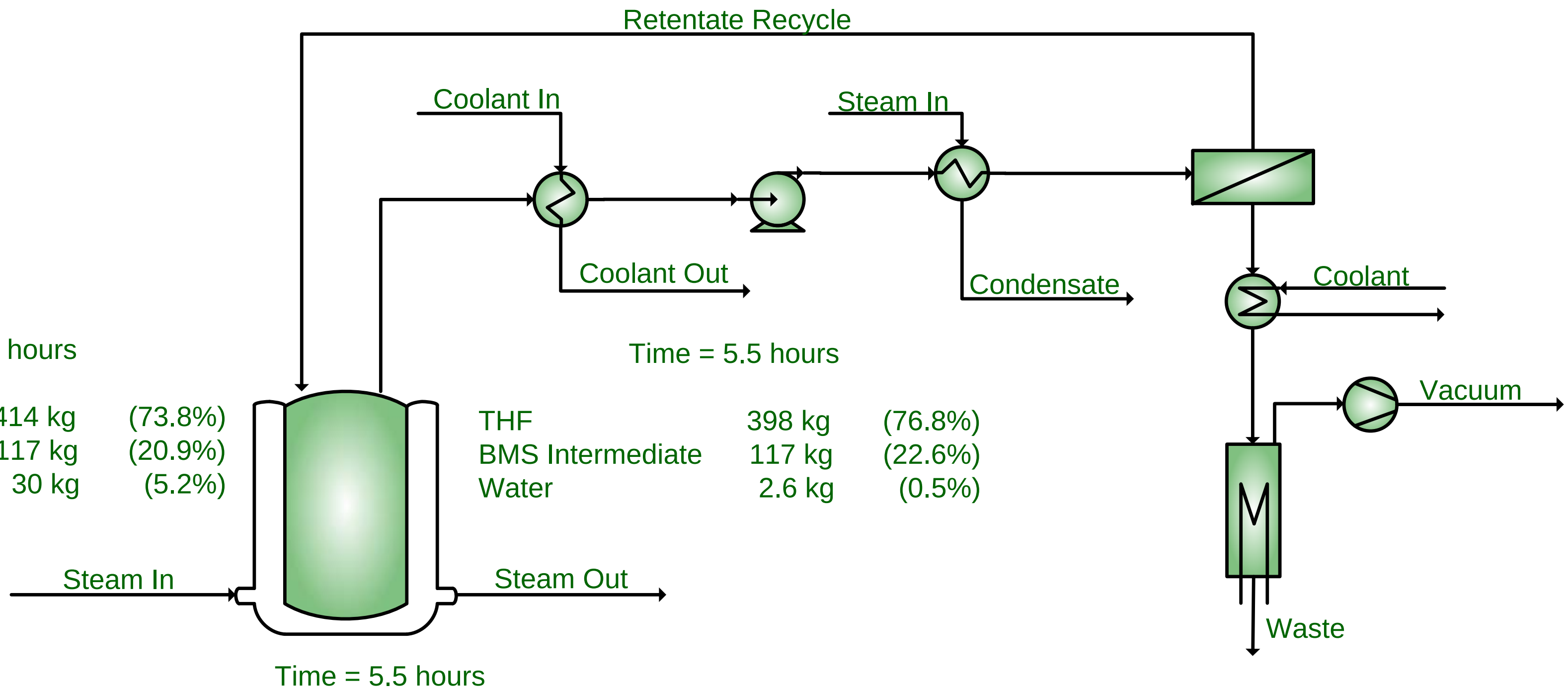
# Design Proposal CVD-PV Integration

## 68 kg API Batch Pilot-Scale




Time = 0 hours

| | | |
|---|---|---|
| THF | 414 kg | (73.8%) |
| BMS Intermediate | 117 kg | (20.9%) |
| Water | 30 kg | (5.2%) |

Time = 5.5 hours

| | | |
|---|---|---|
| THF | 398 kg | (76.8%) |
| BMS Intermediate | 117 kg | (22.6%) |
| Water | 2.6 kg | (0.5%) |

6.1 kg THF/kg API
0.65 kg Waste/kg API
0 kg THF Entrainer/kg API

Time = 5.5 hours

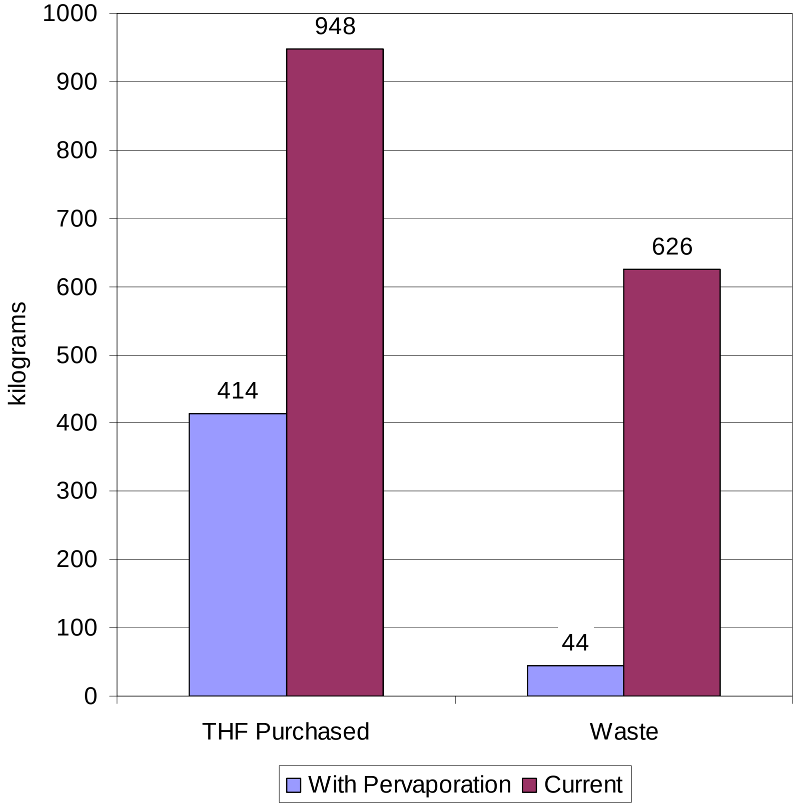
| | | |
|---|---|---|
| THF | 16.5 kg | (95.6%) |
| Water | 27.4 kg | (4.4%) |
| | | |
| Total Waste | 43.9 kg | |

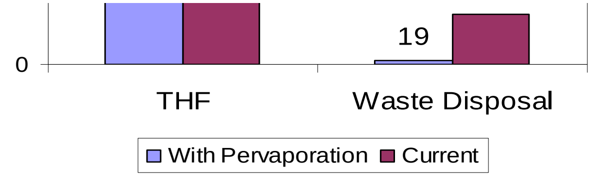
# Design Analysis

- Model proposed CVD-PV system
  - CVD simulation with PV system model
  - Time, Steam usage, Condenser heat duty, Electricity, Various membrane areas
- Compare CVD to CVD-PV
  - Added PV - Utilities
  - Reduction in “Additional THF” entrainer
  - Reduction in waste
- Analyze processes using LCA

*Courtesy of Sulzer Chemtech*

- Reductions in THF used and waste produced
- Environmental savings
- Cost savings

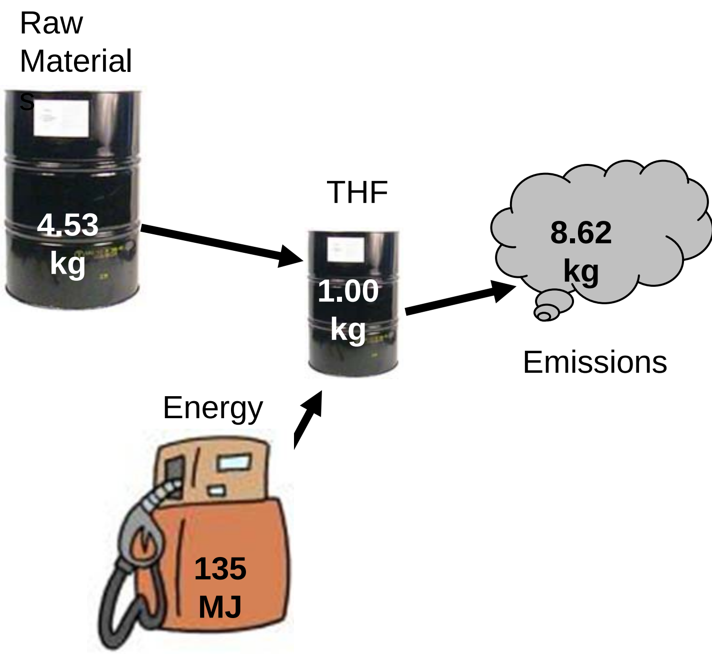



- But this is only one part of story

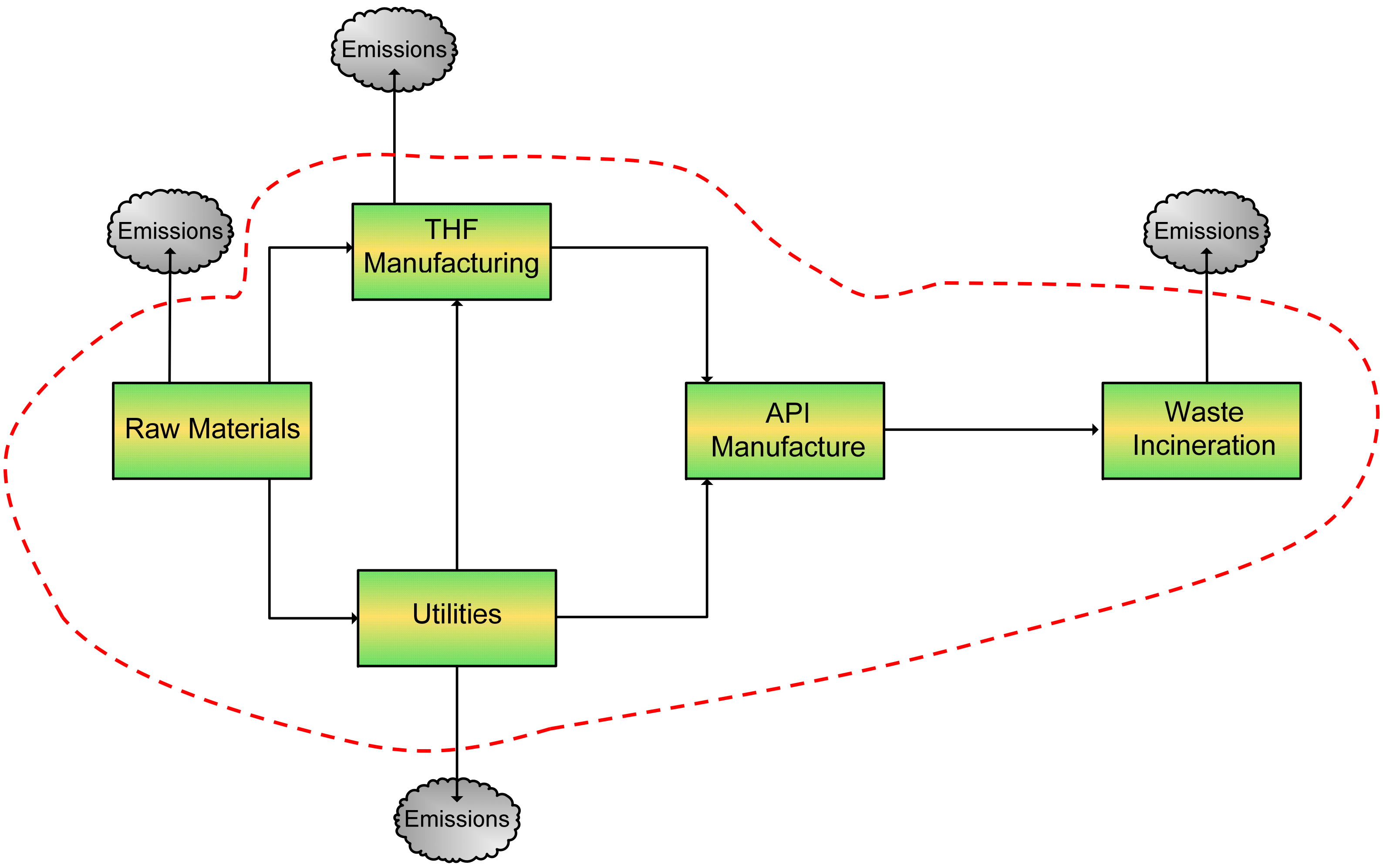
# Environmental Footprint Analysis (LCA)

- Life Cycle Analysis on THF
  - Chemical Tree adapted from Jimenéz-González et al.
  - SimaPro 7.0® utilization with additional data sources
- Additional SimaPro analyses
  - Steam inventory
  - Electricity inventory
  - Analysis on common solvents
- Ecosolvent® analysis on waste treatment




*Jimenéz-González et al., "Expanding GSK's Solvent Selection Guide – application of life cycle assessment to enhance solvent selections", Clean Tech Environ Policy, 7, 42-50, 2005.*

# LCA System Boundaries

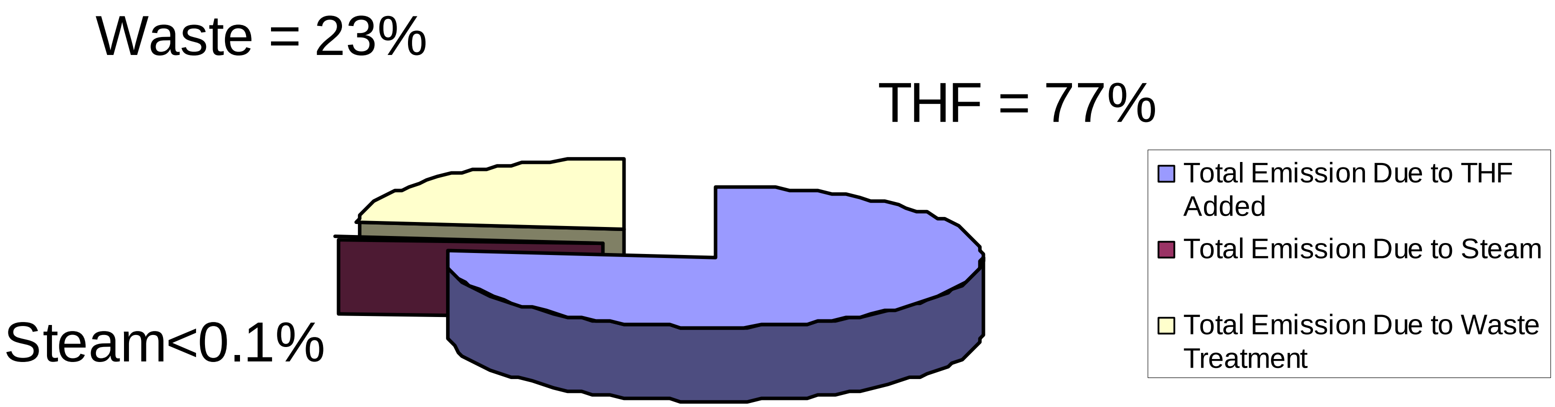


# Environmental Footprint Analysis

## Pilot Scale

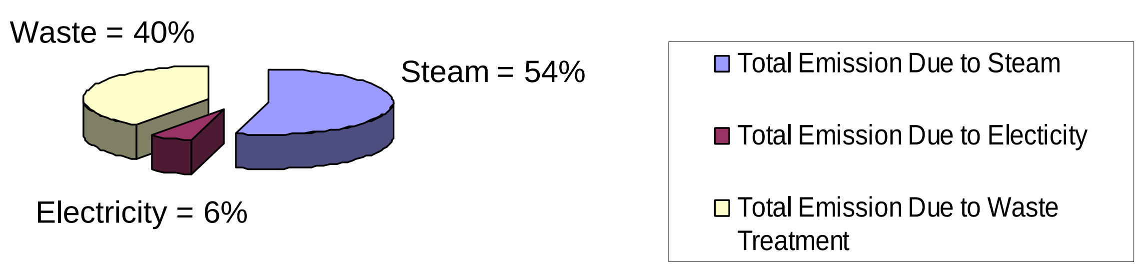
Total CVD Emissions: 6040 kg (89 kg/kg API)

CVD




Total CVD-PV Emissions: 243 kg (3.6 kg/kg API)

CVD-PV



# Economic Analysis Methodology

| | |
|---|---|
| Capital Investment ($) | $560,000 |
| Depreciation Period (years) | 10 |
| Minimal Rate of Return (%) | 17% |
| Cost of Membrane Replacements (three 35 $m^2$ modules@$35K/module every 3 years) | $105,000 |
| Cost of THF ($/kg) | 3.9 |
| Cost of Steam ($/t) | 5.5 |
| Cost of Coolant ($/kWh) | 0.02 |
| Cost of Electricity ($/kWh) | 0.05 |
| Cost of Waste Disposal ($/kg) | 0.43 |

*PV system and membrane information provided by Sulzer, 2007*
*Cost of THF and Waste Disposal provided by BMS, 2007*
*Cost of Steam, Coolant, and Electricity estimated from Peters et al. Plant Design Econ Chem Eng, 2003*

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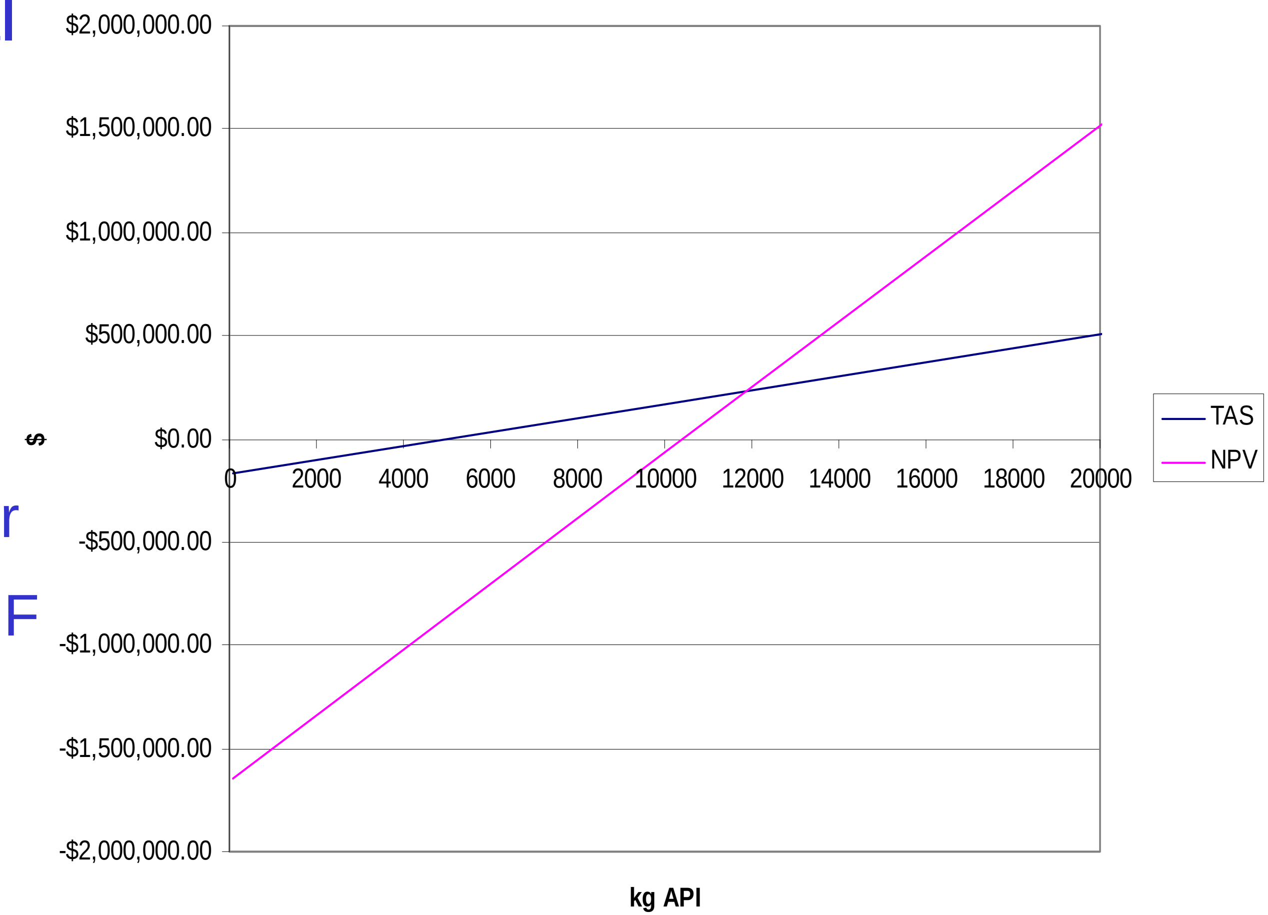
# Economic Analysis

- Not economical at pilot scale
- Economic feasibility TAS=NPV
  - 12,000 kg API/yr
  - 72,000 kg/yr THF or other solvent processed



# P2 Summary for 15,000 kg API/yr (91,300 kg THF)

| | *CVD* | *CVD-PV* | *Reduction* | *% Reduction* |
|---|---|---|---|---|
| **Separation Process** | | | | |
| Process Waste (kg) | 132,000 | 9,700 | 122,300 | 92.7% |
| Energy (kWh) | 45,320 | 207,100 | -161,800 | -358% |
| Annual Operating Costs ($/yr) | $516,000 | $6,850 | $509,150 | 98.7% |
| **LCA (THF Production)** | | | | |
| Total Emissions (kg) | 1,015,400 | 0 | 1,015,400 | 100% |
| Energy, CED (kWh) | 4,425,000 | 0 | 4,425,000 | 100% |
| **LCA (Process Utilities)** | | | | |
| Total Emissions (kg) | 4,500 | 34,000 | -29,500 | -655% |
| **LCA (Waste Incineration)** | | | | |
| Total Emissions (kg) | 311,000 | 22,800 | 288,200 | 92.7% |
| **Total Environmental Summary** | | | | |
| **Total Pollution (kg)** | **1,330,900** | **56,800** | **1,274,100** | **95.73%** |
| **Total Energy (kWh)** | **4,470,000** | **207,118** | **4,262,882** | **95.37%** |
| $CO_2$ Emissions reduction (kg) | | | 1,119,000 | 95.5% |

*Baseline of THF Production is the “Additional THF entrainer” and Total Pollution includes all waste and emissions

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# Summary and Future Plans

- Preliminary design calculations indicate CVD-PV is cost effective and environmentally sound
- Recommendation for BMS to engage vendor in further discussion
- PV approach could replace “Dean Stark” solvent drying on manufacturing scale
- Applicability to other drug API campaigns and solvents

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# Benefits of Partnership

- Publicity/community relations
- Exchange of new Green Engineering ideas
- Industry validates approaches to Green Engineering
- New engineers graduate with knowledge in Green Engineering and pharma industry culture
- University develops expertise to advance state-of-the-art in Green Engineering


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Business

PAGE B4

## Rowan students help make drug production greener

### College partners with Bristol-Myers

By MICHAEL B. BAKER
Staff Writer, (609) 272-7221

MAYS LANDING — A local Rowan University junior is helping a major pharmaceutical company make the manufacturing process for its new cancer-fighting drug more environmentally friendly.

Thor Farnsworth, 21, is among a team of eight Rowan chemical engineering students and faculty members working with New Brunswick-based Bristol-Myers Squibb Pharmaceutical Research on its "green engineering" design.

The term indicates the move to develop products in a way that does not harm the environment or employees while keeping costs reasonable.

For example, the team is looking at ways to replace solvents in the process with materials that are better for the environment, Farnsworth said.

"Sometimes it takes 300 kilograms of solvent to make one kilogram of product," Farnsworth said.

The team also looks at the effects on the pharmaceutical company workers, he said. The members look at health risks to employees, such as ensuring that while trying to help manufacture a product that fights cancer, they themselves are not exposed to carcinogens, he said.

Although the students could have worked with existing drugs, they instead are working on a cancer drug that is in clinical trials and is being made on a pilot scale, according to Stewart Slater, a chemical engineering professor who is one of the project's supervisors. The drug could eventually be used in high volumes.

"To make our work more real-world, Bristol-Myers Squibb said we could be involved in a current project," Slater said in a prepared statement. "We're actually meeting and working with the real team that's developing this drug."

A two-year, $26,813 grant awarded by the U.S. Environmental Protection Agency in October is funding the partnership between Rowan and Bristol-Myers Squibb.

Farnsworth also is involved in the military and will be a commissioned officer when he graduates, he said.

But he eventually plans on attending medical school in New York.

"A lot of people in my family are in medicine," Farnsworth said. "It's always been one of my passions."

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# Acknowledgements

**Bristol-Myers Squibb**

San Kiang

Thomas LaPorte

Lori Spangler

Stephan Taylor

**Rowan University Students**

Timothy Moroz

Colleen McGinness

**U.S. EPA Region 2**

Grant NP97257006-0

Advancing P2 in Pharmaceutical Manufacturing

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# 2008 AIChE Annual Meeting

## *Topical Conference*

## Green Engineering and Sustainability in the Pharmaceutical Industry

**Philadelphia, PA**

**November 16-21, 2008**

Green chemistry & engineering and sustainability are important and timely issues in the pharmaceutical industry. This topical program provides a forum for the discussion of challenges and opportunities which would enable the transition to a sustainable future. These exist in both R&D and manufacturing activities for the API and the finished drug formulation. We expect this topical to be a forum for the exchange of new concepts and ideas between the stakeholders from industry, academia and government. Papers in all areas related to this field are welcome. Requested topics include: benign / safer solvents and recovery practices, batch to continuous processing, pharmaceutical environmental metrics / LCA, green reactions, enzymes and biocatalysis, green and novel separations and methods, commercializing green technology, making the business case for sustainability, sustainable downstream bioprocessing, green engineering with particle technology, green design issues in manufacturing facilities, quality by design, benign by design, PAT, incentives to promote green engineering in the pharmaceutical industry, government programs and partnerships.

**Abstract submissions begin January 15 and end May 14, 2008. Submit electronically through www.aiche.org/Conferences/AnnualMeeting/index.aspx**

**Go to the Topical Conference session of interest.**

**Questions about submitting an abstract? Please contact one of the organizers or session chairs.**

**Organizers: Robert Hesketh (hesketh@rowan.edu), Mariano Savelski (savelski@rowan.edu), C. Stewart Slater (slater@rowan.edu), Rowan University**

**Co-Organizers: David Constable, GlaxoSmithKline and Ann Lee-Jeffs, Johnson & Johnson**

**Sponsored in part by a grant from EPA Region 3: X9-97348001-0**

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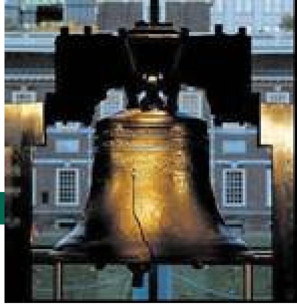
# 2008 AIChE Annual Meeting



- ***Green Engineering Topical Session Listing***

| Session | Chair | | Co-Chair | |
|---|---|---|---|---|
| Batch to Continuous Pharmaceutical Processing Challenges | Daniel R. Pilipauskas, Pfizer | daniel.pilipauskas@pfizer.com | Fernando J. Muzzio, Rutgers | muzzio@soemail.rutgers.edu |
| Benign / Safer Solvents in Pharmaceutical Processing | David J. C. Constable, GSK | David.c.constable@gsk.com | Sanjeev Katti, Genzyme | sanjeev.katti@genzyme.com |
| Government Programs and Partnerships | Nhan Nguyen, EPA | nguyen.nhan@epa.gov | Richard E. Engler, EPA | engler.richard@epa.gov |
| Green Engineering and Sustainability in the Pharmaceutical Industry | Robert P. Hesketh, Rowan | hesketh@rowan.edu | Mariano J. Savelski, C.Stewart Slater, Rowan | savelski@rowan.edu, slater@rowan.edu |
| Green Reactions in the Pharmaceutical Industry | Kim Albizati, BioVerdant | kim.albizati@bioverdant.com | Sanjeev Katti, Genzyme | sanjeev.katti@genzyme.com |
| Green Separations in the Pharmaceutical Industry | Alexander J. Marchut, Brsitol-Myers Squibb | alexander.marchut@bms.com | Mahmoud El-Halwagi, Texas A&M Univ | el-halwagi@tamu.edu |
| Pharmaceutical Environmental Metrics / | Concepcion Jimenez-Gonzalez, GSK | conchita.j.gonzalez@gsk.com | | |
| The Business Case for Sustainability in the Pharmaceutical Industry | Ann Lee-Jeffs, Johnson & Johnson | aleej@corus.jnj.com | John Leazer, Merck | john_leazer@merck.com |